IN THE UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF MISSOURI
WESTERN DIVISION

MAX RIDINGS, ET AL.	)	
	)	
Plaintiffs,	)	
	)	
v.	)	Case No. 4:15-cv-00020-JTM
	)	
SCOTT MAURICE, ET AL.	)	
	)	
	)	
Defendants.	)	

SUGGESTIONS IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT

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Defendants Boehringer Ingelheim Pharmaceutics, Inc., Boehringer Ingelheim USA Corporation, and Boehringer Ingelheim Corporation (collectively, "BI")[1] move for summary judgment on all of Plaintiffs' claims, including Plaintiffs' request for punitive damages. Plaintiffs' failure to warn claims fail because Dr. Gupta unequivocally stands by his decision to prescribe Pradaxa in the face of all Plaintiffs' failure-to-warn theories. The design defect claims fail because Plaintiffs have not identified a defect in Pradaxa's design. The remaining claims, all flowing from Plaintiffs' central allegations, fail as well.

Plaintiffs' claims separately fail on the basis of federal preemption. Plaintiffs' failure to warn claims are barred because Plaintiffs have not shown information "newly acquired" after Pradaxa's approval supporting a label change, and there is "clear evidence" that the FDA would have rejected Plaintiffs' proposed warnings. Plaintiffs' design defect claims are also preempted because BI could not market a reversal agent for Pradaxa without the FDA's permission.[2]

STATEMENT OF UNDISPUTED FACTS

I. Pradaxa's development and warnings

1. Pradaxa (dabigatran) is a prescription medicine approved by the U.S. Food and Drug Administration ("FDA") in October 2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Compl. ¶ 20.

2. Pradaxa is marketed in the United States by BI, whose principal place of business is located in Ridgefield, Connecticut. Compl. ¶ 24.

[1] Defendants Boehringer Ingelheim USA Corporation and Boehringer Ingelheim Corporation have no involvement with the design, testing, manufacture, marketing sale, labeling, promotion, or any other aspect of Pradaxa. Defendant Boehringer Ingelheim International GmbH is named in the Complaint, but has not been served with process.

[2] Defendants filed a Motion for Enlargement of Page Limitation on May 6, 2019 [Dkt. 77], but have not received a ruling on that motion. Plaintiffs have indicated they do not object to the additional pages. Should the Court find that BI is not entitled to additional pages, BI will submit a revised brief in conformance with L.R. 7.0(d).

3. Prior to Pradaxa's approval, BI submitted comprehensive safety and efficacy information to the FDA as part of the Pradaxa New Drug Application ("NDA"), including data and analyses regarding the same risks that Plaintiff now relies upon for his failure-to-warn allegations:

- Rates of various types of bleeding observed with Pradaxa in RE-LY and other clinical trials, *see, e.g.*, Ex. 1, Boehringer Ingelheim, Clinical Overview, at 62–68 (Nov. 10, 2009) (BIPI-PRA-0001190542);
- The risk of bleeding with Pradaxa in elderly patients, *see, e.g.*, *id*. at 70–73;
- The risk of bleeding in patients with impaired renal function, *see, e.g., id.*;
- The risk of bleeding based on patient weight, *see, e.g., id*. at 70–72; and
- The risk of bleeding based on various other patient characteristics, including concomitant medications, *see, e.g., id*. at 75–77.

4. During the FDA review process, BI communicated extensively with the FDA regarding the relationship between Pradaxa blood plasma concentrations and bleeding risk, and whether routine monitoring of Pradaxa blood plasma levels or dose adjustments guided by such monitoring might improve Pradaxa's benefit-risk profile. *See, e.g., id*. at 23–25, 30–35, 94. As part of the NDA, BI submitted all of the RE-LY data on plasma concentrations and analyses regarding the relationship between plasma concentrations and patient outcomes. *Id*.

5. As part of this process and after, warnings now proposed by Plaintiff were submitted to the FDA by BI and specifically rejected by the FDA.

6. Prior to approving Pradaxa, the FDA carefully reviewed BI's submissions, undertook its own independent analyses of the RE-LY trial data, and issued numerous memos detailing its multi-disciplinary review of the medicine's safety and efficacy. *See, e.g.*, Ex. 2, FDA Ctr. For Drug Evaluation & Res., Application No. 22-512 Summary Review (Oct. 19, 2010); Ex. 3, FDA Ctr. for Drug Evaluation & Res., Application No. 22-512 Office Director

Memo (Oct. 14, 2010); Ex. 4, FDA Ctr. for Drug Evaluation & Res., Application No. 22-512 Medical Review(s) (Sept. 2, 2010); Ex. 5, FDA Ctr. for Drug Evaluation & Res., Application No. 22-512 Clinical Pharmacology and Biopharmaceutics Review(s) (Sept. 1, 2010). These memos discussed Pradaxa's risks, including the increased risk of bleeding, *see, e.g.*, Ex. 2, Summary Review, at 10–11; and the impact of patient characteristics like age, renal function, weight, and concomitant medications on Pradaxa's safety, *see, e.g.*, Ex. 5, Clinical Pharmacology and Biopharmaceutics Reviews, at 9–12; Ex. 3, Office Director Memo, at 3. The FDA's clinical pharmacologists also analyzed, in particular, the relationship between plasma concentration and patient outcomes and considered whether this suggested a need for monitoring plasma concentration and adjusting the dose of Pradaxa based on such measurements. *See, e.g.*, Ex. 5, Clinical Pharmacology and Biopharmaceutics Review(s), at 9, 17–18; Ex. 3, Office Director Memo, at 1–2.

7. As part of its pre-approval deliberations, in September 2010, the FDA convened an Advisory Committee of independent experts to review Pradaxa's safety and efficacy. Ex. 2, Summary Review, at 16. At the Advisory Committee meeting, both the FDA and BI presented their analyses of the relationship between plasma concentration and patient outcomes. *See, e.g.*, Ex. 6, Kevin Krudys, Exposure Response Analysis of Dabigatran in RE-LY (Sept. 20, 2010). When one of the meeting participants raised the possibility of monitoring plasma concentrations, Dr. Krudys, the FDA Pharmacometrics Reviewer presenting on behalf of the FDA, responded that the FDA saw no need for such monitoring given Pradaxa's favorable safety-efficacy profile across all subgroups.

> DR. MCGUIRE: Okay. Then, Dr. Krudys, I have some questions about your dose response relationships. I'm struck by what my eyeball tells me is about a five-fold variability within 90 percent confidence of the 150-dose with regards to the steady state concentration achieved. That seems awfully big to me in a drug that we're

> proposing to use without any therapeutic monitoring. So can you put this in the context of other anti-thrombotic therapies? Is this a usual variability inter-patient, and also ***does this speak toward possibly considering therapeutic monitoring of some sort?***
>
> DR. KRUDYS: As relative to other drugs, I'm not sure myself, but I can say for this drug there are certain factors. Renal function, like I said, could change concentrations two-fold. Drug interactions, we saw, could change it 20 to 40 percent. So there are some factors that will change concentrations quite a bit, but ***we didn't see a need for . . . monitoring the concentration because we saw in a study, favorable results in all subgroups. So it didn't seem like we found something strong that we needed to monitor concentrations and adjust in a certain subset of the population.***

Ex. 7, FDA Ctr. for Food and Drug Evaluation & Res., Cardiovascular & Renal Drugs Advisory Comm. Tr. 163:18–164:16 (Sept. 20, 2010).

8. On October 2010, the FDA approved Pradaxa at a dose of 150 mg to reduce the risk of stroke in patients with non-valvular atrial fibrillation. Ex. 8, FDA Ctr. for Food and Drug Evaluation & Res., NDA 022512 Approval Letter (Oct. 19, 2010).[3] At this time, the FDA approved Pradaxa's launch label, including the warning that "PRADAXA can cause serious and, sometimes, fatal bleeding," as well as additional warnings based on age, renal impairment, and concomitant medications. Ex. 9, Pradaxa Label, at 1 (Oct. 2010). The FDA approved Pradaxa without any requirement for monitoring plasma concentrations or adjusting dosage based on such monitoring. *See, e.g.*, Ex. 8, NDA 022512 Approval Letter; Ex. 3, Office Director Memo, at 4 ("Follow-up of anticoagulant activity is generally not needed."). At the same time, and at several points thereafter, the FDA rejected BI's request for approval of a lower 110 mg dose, in the process rejecting labeling proposals that would guide physicians to use the 110 mg dose in certain instances. *See, e.g.*, Ex. 8, NDA Approval Letter; Ex. 2, Summary Review, at 2. In the more than eight years following Pradaxa's approval, the FDA has approved Pradaxa's U.S.

[3] Additionally, a 75 mg dose was approved for patients with severely impaired renal function. Ex. 8, NDA Approval Letter.

labeling on 18 separate occasions.[4] During this time, the FDA has issued numerous other statements reaffirming Pradaxa's safety and efficacy when used as directed by the U.S. label, without any requirement for plasma monitoring or dose adjustment.[5]

9. The Pradaxa label in effect at the time of Mr. Ridings' prescription specifically warned that "PRADAXA can cause serious and, sometimes, fatal bleeding" and that bleeding was one of the "[m]ost common adverse reactions." Ex. 11, Pradaxa (Jan. 2012) label at 1 (emphasis added).

10. The label clearly and unequivocally warned of the risk of bleeding, including intracranial hemorrhage, intracerebral hemorrhage, hemorrhagic stroke, subarachnoid and subdural bleeds. *Id*. at § 6.1.

11. The Warnings and Precautions section repeats that "PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding." *Id.* at § 5.1.

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[4] *See* Ex. 10, FDA, *Drugs@FDA: FDA Approved Drug Products*, http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022512 (last accessed May 6, 2019)

[5] *See, e.g.*, Ex. 12, Ellis F. Unger, *Atrial Fibrillation, Oral Anticoagulant Drugs, and Their Reversal Agents*, FDA (Oct. 16, 2015), https://www.fda.gov/drugs/newsevents/ucm467203.htm ("We are constantly examining patient safety data and conducting other surveillance activities after products are on the market to ensure that the labels reflect current knowledge with regard to benefits and risks. . . . Based on this evaluation, FDA has not changed its recommendations regarding the use of Pradaxa; it provides an important health benefit when used as directed."); Ex. 13, FDA, *Drug Safety Communication: FDA Study of Medicare Patients Finds Risks Lower for Stroke and Death but Higher for Gastrointestinal Bleeding with Pradaxa (Dabigatran) Compared to Warfarin* (May 13, 2014), https://www.fda.gov/Drugs/DrugSafety/ucm396470.htm ("As a result of our latest findings, we still consider Pradaxa to have a favorable benefit to risk profile and have made no changes to the current label or recommendations for use."); Ex. 14, Mary Ross Southworth et al., *Dabigatran and Postmarketing Reports of Bleeding*, 368 N. Eng. J.Med. 1272, 1274 (2013) (article by three FDA authors concluding that "[w]e believe that dabigatran provides an important health benefit when used as directed"); Ex.15, FDA, *Drug Safety Communication: Update on the Risk for Serious Bleeding Events With the Anticoagulant Pradaxa (Dabigatran)* (Nov. 5, 2012) ("FDA has not changed its recommendations regarding Pradaxa. Pradaxa provides an important health benefit when used as directed. Healthcare professionals who prescribe Pradaxa should carefully follow the dosing recommendations in the drug label"); Ex. 16, Nhi Beasley et al., *Anticoagulant Options—Why the FDA Approved a Higher but Not a Lower Dose of Dabigatran*, 364 N. Eng. J. Med. 1788, 1789 (2011) (article by three FDA authors concluding that "even in a population exposed to relatively high concentrations of dabigatran, the 150-mg dose had a superior benefit–risk profile").

12. The Drug Interactions section notes that taking P-gp inhibitors is a "major independent factor[]" that can "result in increased exposure to" Pradaxa. *Id*. at § 7.

13. The label states: "[a] specific reversal agent for dabigatran is not available;" and "[t]here is no reversal agent for dabigatran." *Id*. at §5.1; §10.

II. Mr. Ridings's Pradaxa use and lawsuit.

14. In February, 2012, Mr. Ridings's treating cardiologist, Dr. Sanjaya Gupta, prescribed him to take 150mg of Pradaxa twice daily to reduce his risk of stroke due to atrial fibrillation. Ex. 17, Sanjaya Gupta, M.D. (5/14/18) Dep. at 7:2-9; 90:9-12; 98:12-13.

15. Atrial fibrillation is a heart rhythm abnormality that allows blood to pool within the heart, which then can develop blood clots that can be ejected from the heart, thus increasing a person's risk of developing a stroke by five times. *Id*. at 26:9-20; 27:7-20.

16. Dr. Gupta reviewed the product warnings when Pradaxa came out in 2010, but did not re-review it prior to prescribing Pradaxa for Mr. Ridings. Ex. 17, Sanjaya Gupta (11/18/15) Dep. at 256:9-14.("Q. You reviewed this information, correct, in -- when -- prior to describing Pradaxa to Mr. Ridings; correct? A. I -- I reviewed it when Pradaxa came out, when the drug came out. I didn't re-review it prior to my -- my prescribing of him that day.").

17. At the time that he prescribed Pradaxa to Mr. Ridings, Dr. Gupta knew: that Pradaxa could cause serious and sometimes fatal bleeding (Ex. 17, Gupta (5/14/18) Dep. at 49:14-18) or an intracerebral hemorrhage (*id*. at 49:19-22); that Pradaxa was available only in fixed doses of 75mg and 150mg (*id*. at 50:12-15; 71:21-23); that aPTT (activated prothrombin time) or ECT (ecarin clotting time) values can tell you only if someone is taking Pradaxa, but those tests do not measure therapeutic range (*id*. at 52:4-25); that concomitant use of aspirin could increase the risk of bleeding on Pradaxa (*id*. at 54:10-18); and that renal impairment could increase the risk of bleeding on Pradaxa (*id*. at 55:1-9).

18. When he prescribed Pradaxa to Mr. Ridings, Dr. Gupta also knew there was no reversal agent for Pradaxa. *Id*. at at 60:17-21 ("Q. And you understood at the time you prescribed Pradaxa for Mr. Ridings that there was no reversal agent or antidote available to reverse the anticoagulant effect of Pradaxa? A. Correct.").

19. Dr. Gupta knew that the label states that P-gp inhibitors are a factor in potential increased exposure to Pradaxa, but he is not aware of any clinically convincing evidence to this effect that would have changed his decision to prescribe Pradaxa to Mr. Ridings. Ex. 17, Gupta Dep. (11/15/18) at 233:12-22; 265:18–266:12.

20. When presented with an article from the Canadian Medical Association regarding a claimed increase in bleed risk in patients using simvastatin (a P-gp inhibitor) and Pradaxa, Dr. Gupta testified it would not have changed his opinion to prescribe Pradaxa to Mr. Ridings. *Id*. at 249:1-11 ("Q. Having read this article that's been marked as Plaintiff's Exhibit 3, does it change your decision about having prescribed Pradaxa for Mr. Ridings in 2012? A. No. No. Q. Do you -- after having seen this article and been asked questions about it, do you stand by your decision to have prescribed Pradaxa for Mr. Ridings in 2012 and 2013? A. Yes.") (counsel objection omitted).

21. In determining if a patient should be placed on anticoagulation therapy, Dr. Gupta weighs risks of bleeding, including the risk of an intracranial hemorrhage and any potential outcome of that condition, against the benefit of stroke prevention. Ex. 17, Gupta (5/14/18) Dep. at 83:24–84:13.

22. Dr. Gupta believes that Mr. Ridings was an appropriate candidate for Pradaxa and that the benefits outweighed the risks for him. *Id*. at 102:18-25 ("Q. Did you believe that Mr. Ridings was an appropriate candidate for Pradaxa at the time of the February 9th, 2012,

appointment? A. Yes. Q. And did you believe that the benefits of Mr. Ridings taking Pradaxa outweighed its risks? A. Yes.").

23. Dr. Gupta stands by his decision to prescribe Pradaxa for Mr. Ridings. *Id*. at 130:24–131:3 ("Q. Okay. Knowing that Mr. Ridings sustained a subdural hematoma, do you still stand by your decision to have recommended that he take Pradaxa? A. I do.").

24. Dr. Gupta still prescribes Pradaxa to his patients. *Id*. at 23:22-23.

25. On July 31, 2013, Mr. Ridings was admitted to the hospital for a subdural hematoma. Stephen Griffith, M.D. (3/1/19) Dep. at Ex. 5.

26. A subdural hematoma is a collection of blood under the dura, one of the outer linings of the brain adjacent to the skull. Ex. 17, Gupta (5/14/18) Dep. at 82:15-18.

27. Dr. Stephen Griffith, the neurosurgeon who treated Mr. Ridings for his subdural hematoma, consulted with the hospital pharmacist concerning the length of time required for Pradaxa to "wash out of his system," and accordingly scheduled Mr. Ridings's surgery for burr hole placement to insert a subdural drain for August 2, 2013. Ex. 18, Griffith (3/1/19) Dep. at 31:10-23; 33:10-25.

28. After replacing one drain that had become clogged, Dr. Griffith removed the subdural drain on August 7, 2013. *Id*. at 36:5-15; 37:15–38:4.

29. Thereafter, Mr. Ridings became less responsive, and he was determined to have a tension pneumocephalus, a condition where air pressure builds within the skull and can cause serious injury. *Id*. at 39:16–40:22.

30. Because of the development of this condition, Dr. Griffith performed a craniotomy on August 9, 2013, to remove "chronic subdural membranes" that "were sequestering the brain." *Id*. at 41:24–42:13.

31. Mr. Griffith was brought to surgery again later that same day for a second craniotomy. *Id*. at 44:19–45:20.

32. Following his hospitalization for the subdural hematoma, according to Dr. Griffith, "Mr. Ridings has done fantastic postoperatively. His head CT was reviewed today. His subdural collection has resolved. His brain has expanded to fill the space necessary. On exam he is neurologically intact and doing wonderfully." *Id*. at 18:10-14.

33. Plaintiffs filed this lawsuit on December 10, 2014, asserting claims arising from Mr. Ridings's bleeding event, including claims for strict liability failure to warn, strict liability design defect, negligence, express warranty, implied warranty, Missouri Merchandising Practices Act, fraudulent concealment[6], negligent or fraudulent misrepresentation, and loss of consortium, and they seek punitive damages as part of their requested relief. *See generally,* Complaint.

BACKGROUND

Pradaxa (dabigatran) is an oral anticoagulant approved to reduce the risk of stroke in patients suffering from atrial fibrillation. Atrial fibrillation results in an irregular heartbeat that may cause blood to pool in the heart's chambers and form a clot that can dislodge and move to the brain, causing a stroke. In lay terms, Pradaxa works by thinning the blood and inhibiting clotting, thereby reducing the risk of stroke.

Pradaxa, like all anticoagulants, increases a patient's risk of bleeding. For this reason, BI has always warned prominently about the risk of bleeding from Pradaxa, including by using the following front-page warning since launch: "PRADAXA can cause serious and, sometimes, fatal bleeding." Ex. 9, Pradaxa Label (Oct. 2010) at 1. Physicians prescribe Pradaxa and other

[6] Fraudulent concealment in Missouri prevents a defendant from relying on the statute of limitations if he affirmatively intended to conceal from the plaintiff that the plaintiff had a claim against him. *Batek v. Curators of Univ. of Missouri*, 920 S.W.2d 895, 900 (Mo. 1996). Given that Defendant has not asserted a statute of limitations defense, this doctrine is not relevant here.

oral anticoagulants notwithstanding this risk because they recognize that the benefits of preventing debilitating and often fatal strokes far outweigh the risk of bleeding.

Like almost all medicines, Pradaxa is prescribed at a fixed dose, without any requirement to test patient blood levels to determine if dose adjustments are necessary based on the amount of medicine circulating in the patient's bloodstream. Nevertheless, well before Pradaxa's approval, scientists and regulators evaluated whether Pradaxa's risk-benefit profile could be improved through blood plasma testing and corresponding dose adjustments aimed at maintaining plasma levels within a hypothesized target therapeutic range.

Scientists, including those employed by BI, have advanced various hypotheses about what a target range might be, and how the dose might be adjusted to reach that range. But intensive study has led scientists to conclude that no optimal range or perfect dose adjustment strategy exists. Every regulatory agency in the world agrees, approving Pradaxa on a fixed-dose basis, without monitoring blood plasma levels and adjusting dosages.

ARGUMENT

I. General Legal Standards.

A. Missouri law applies to Plaintiffs' substantive claims.

Plaintiffs are residents of Missouri and have been at all times pertinent to the allegations in the Complaint. Compl. at ¶¶ 1-2. Mr. Ridings was prescribed Pradaxa and received treatment for the injuries he claims were caused by Pradaxa in Missouri. Compl. ¶ 61.

Missouri applies the "most significant relationship" test of the Restatement (Second) of Conflict of Laws. *See Estate of Nixon v. Gov't Employees Ins. Co.*, 954 F. Supp. 2d 894, 898 (W.D. Mo. 2014) (citing *Kennedy v. Dixon*, 439 S.W.2d 173, 184 (Mo. 1969) (en banc)). As the place of Plaintiffs' residence, the state where he was prescribed and ingested Pradaxa, and the

state where he claims to have suffered injury, Missouri has the most significant relationship to this case and its substantive law should apply here.

B. Summary Judgment Standard.

The Court may grant summary judgment "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). The burden of establishing the absence of a genuine issue of material fact lies with the moving party. *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986). The movant "bears the initial responsibility of informing the district court of the basis for its motion, and identifying those portions of [the record] which it believes demonstrate the absence of a genuine issue of material fact." *Celotex Corp.*, 477 U.S. at 323. After the movant has met its burden under Rule 56(a), the burden of production shifts and the nonmoving party "must do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita Electronic Industrial Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986). Essentially, the non-moving party must come forward with affirmative evidence to support its claim. *Anderson*, 477 U.S. at 257; *Earley v. Champion Int'l Corp.*, 907 F.2d 1077, 1080 (11th Cir. 1990). Conclusory, uncorroborated allegations will not create an issue of fact for trial sufficient to defeat a well-supported summary judgment. *See Earley*, 907 F.2d at 1081.

II. Plaintiffs Lack Proof of a Design Defect, and Any Claim Based on Design Defect Is Preempted.

To prevail on their negligent or strict liability design defect claims, Plaintiffs must prove a defect specific to the design of the product at issue. *Nesselrode v. Executive Beechcraft, Inc.*, 707 S.W.2d 371, 375-76 (Mo. Ct. App. 2008) ("[T]he plaintiff bears the burden of demonstrating that the product, as designed, is unreasonably dangerous and therefore 'defective', and that the

demonstrated defect caused his injuries."). Plaintiffs have no such proof here, whether alleged under strict liability or negligence.

A. Lack of a reversal agent is not a design defect for Pradaxa.

To the extent that Plaintiffs allege that Pradaxa was defective because it originally lacked a reversal agent, this argument fails. *See* Compl. ¶¶ 30, 32, 36, 41, 59. 85. A reversal agent (Praxbind) is not a "design" for Pradaxa. Rather, it is a separate "biologic" product that required FDA approval prior to being marketed and used for clinical purposes. *See* 42 U.S.C. § 262(a), (j). As two federal courts held in Pradaxa cases, "Plaintiff may not establish a design defect of *Pradaxa* by pointing to the failure to develop *Praxbind*. . . . Praxbind is not a part of Pradaxa's design, but rather is a different drug requiring separate FDA approval." *See Chambers v. Boehringer Ingelheim Pharms., Inc.*, No. 4:15-CV-00068 (CDL), 2018 WL 849081, at *13, (M.D. Ga. Jan. 2, 2018); *Knight v. Boehringer Ingelheim Pharms., Inc.*, 323 F. Supp. 2d 809, 834 (S.D.W. Va. 2018) ("This Court agrees with both the reasoning and conclusion of the *Chambers* court."). The *Chambers* court further found there was no evidence that the failure to develop Praxbind caused any injury. *Chambers*, 2018 WL 2470990, at *13. Similarly, the court overseeing the Connecticut coordinated Pradaxa litigation also found that Praxbind "is a different product as a matter of law and not a design element of Pradaxa." *See* Ex. __, Order re 125.000 Motion for Summary Judgment, *Boone v. Boehringer Ingelheim Pharms.*, No. HHDCV166067796S (Sup. Ct. Conn. Jan. 24, 2018). The same result is proper here, and Plaintiffs' design-defect claims should be dismissed.

B. Alternatively, Plaintiffs' design-defect claims are preempted by federal law.

Separately, Plaintiffs' design-defect claim should also be dismissed on the grounds that any such claim is preempted by federal law because BI could not redesign Pradaxa or market a reversal agent without prior FDA approval. *See Mutual Pharm. Co., Inc. v. Bartlett*, 133 S. Ct.

2466, 2471 (2013). This was the conclusion of other courts addressing this same issue in *Chambers* and *Boone* and should also hold here.

The Supreme Court has held that a claim is preempted "when a party ***cannot satisfy its state duties without the Federal Government's special permission and assistance***." *PLIVA, Inc. v. Mensing* (2011) 564 U.S. 604, 623-24 (emphasis added). Therefore, when an entity is not permitted under federal law to *unilaterally* comply with duties imposed by state tort law claims, those state law claims are preempted by federal law. Further, the Supreme Court has specifically recognized that federal law prohibits drug manufacturers from altering the drug formulation without prior FDA approval. [7]

Here, any design-defect claim is preempted because BI could not redesign Pradaxa, alter its formulation, or market a reversal agent without prior FDA approval.

The FDA approved Pradaxa without any requirement that it be marketed or used with a reversal agent; indeed, the FDA-approved label specifically warned that Pradaxa had no reversal agent. SUF ¶ 13. Before the Pradaxa reversal agent could be marketed and used for clinical purposes, it had to first be approved by the FDA. *See* 42 U.S.C. § 262(a), (j). The reversal agent was not approved by the FDA until October 2015. To the extent that Plaintiffs' design-defect claim is based on the unavailability of the reversal agent at the time of Mr. Ridings's bleed, Plaintiffs seek to impose a state-law duty on BI to have brought the reversal agent to market prior to FDA approval. But BI "cannot independently satisfy those state duties for pre-emption purposes." *Mensing*, 564 U.S. at 624.

[7] *Mutual Pharm. Co., Inc. v. Bartlett* (2013) 133 S. Ct. 2466, 2471 (quoting 21 C.F.R. § 314.70(b)(2)(i)) ("Once a drug -- ***whether generic or brand-name*** -- is approved, the manufacturer is prohibited from making any major changes to the 'qualitative or quantitative formulation of the drug product, including [in]active ingredients, or in the specifications provided in the approved application.'").

Because BI could not have secured approval of a reversal agent or changed Pradaxa's design to require that it be used alongside a reversal agent without first getting FDA approval, any state-law claims based on BI's failure to do so are preempted.

The court overseeing the Connecticut coordinated litigation and the federal court in *Chambers* both concluded that any claim related to lack of reversal agent was preempted by federal law. *See* Ex. 19, Order, *Boone v. Boehringer Ingelheim Pharmaceuticals, Inc., et al.*, No. HHDCV1660677968 (Conn. Super. Ct. Jan. 24, 2018) (granting summary judgment as to plaintiff's design-defect claims because, among other reasons, any claim that BI should have developed a reversal agent for Pradaxa was preempted under federal law); *Chambers*, 2018 WL 849081, at *13 ("Boehringer could not unilaterally offer Praxbind to physicians. Therefore, initiating the process that may have led to Praxbind's approval does not enable Boehringer to comply with both federal and state law. Further, Boehringer was not required to cease production of Pradaxa until Praxbind was approved to comply with federal and state law.").

The impossibility of altering the design or formulation of Pradaxa or marketing a reversal agent without prior FDA approval leaves Plaintiffs with the argument that, to avoid state-law liability, BI should have stopped selling Pradaxa altogether until it secured such FDA approval. The Supreme Court, however, has squarely rejected this argument that a drug manufacturer could comply with both federal and state law by simply ceasing to sell the drug in question: the Court's "pre-emption cases presume that an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability. Indeed, if the option of ceasing to act defeated a claim of impossibility, impossibility pre-emption would be 'all but meaningless.'" *Bartlett*, 133 S. Ct. at 2477 (quoting *Mensing*, 564 U.S. at 621); *see also*

Yates, 808 F.3d at 300 ("We reject this never-start selling rationale for the same reasons the Supreme Court in *Bartlett* rejected the stop-selling rationale").

Because federal law prohibited BI from unilaterally altering Pradaxa's design in the ways that Plaintiffs suggest, Plaintiffs' design-defect claim fails as a matter of law. The FDA approved Pradaxa—without a reversal agent—as safe and effective. The FDA concluded that Pradaxa should be available for patient use, making this judgment based on scientific data supporting Pradaxa's safety and efficacy. A state-law rule that Pradaxa must be sold with another design or with a reversal agent would obstruct the FDA's exercise of its authority—as established by Congress—to provide this range of safe and effective medication options. For this additional reason, any design-defect claim is preempted.

III. Because Dr. Gupta Was Aware of the Risks and Stands by His Decision to Prescribe Pradaxa to Mr. Ridings, Plaintiffs Cannot Establish a Failure to Warn Claim or Any Other Claim that Relies Upon Such Evidence.

To establish a claim for failure to warn, Plaintiffs must show that (1) the defendant designed the product at issue; (2) the product did not contain an adequate warning of the alleged defect or hazard; (3) the defendant failed to use ordinary care to warn of the risk of harm from the alleged defect or hazard; and (4) as a direct result of the defendant's failure to adequately warn, the plaintiff sustained damage. *See Moore v. Ford Motor Co.*, 332 S.W.3d 749, 764 (Mo. 2011). In a case involving a prescription drug, Missouri's learned intermediary doctrine requires the manufacturer to warn prescribing doctors, and measures the adequacy of the warning from the perspective of the physician, rather than the patient. *See Doe v. Alpha Therapeutic Corp.*, 3 S.W.3d 404, 419 (Mo. Ct. App. 1999).

Here, Mr. Ridings's prescribing physician, Dr. Sanjaya Gupta, knew of the risk of bleeding associated with Pradaxa, knew there was no reversal agent and knew that P-gp inhibitors could be associated with an increased exposure to Pradaxa, yet he stands by his

decision to prescribe Pradaxa to Mr. Ridings in order to address his significant stroke risk due to atrial fibrillation. *See* SUF ¶¶ 17-23; Plaintiffs cannot establish that any alleged warning deficiency caused any injury, and their failure to warn claim should be dismissed.[8]

A. Dr. Gupta was aware of the risk of bleeding and that there was no reversal agent, so Plaintiffs cannot show that any claimed inadequacy in the label caused any injury.

Under the learned intermediary doctrine, "the causal link between a patient's injury and the alleged failure to warn is broken when the prescribing physician had substantially the same knowledge as an adequate warning from the manufacturer that should have been communicated to him." *Doe v. Miles, Inc.*, 2000 WL 667383, * 13 (Mo. Ct. App. May 23, 2000); *see also Alpha Therapeutic*, 3 S.W.3d at 420 ("learned intermediary doctrine provides that the failure of a drug manufacturer to provide the physician with an adequate warning of the risks associated with a prescription product is not the proximate cause of a patient's injury if the prescribing physician had independent knowledge of the risk that the adequate warnings should have communicated."); *Kirsch v. Picker Intern., Inc.*, 753 F.2d 670, 671-72 (8th Cir. 1985) (holding a manufacturer's alleged failure to warn could not have proximately caused plaintiff's skin cancer because the doctor was aware of the risks).

Here, Dr. Gupta was aware of the risks of bleeding associated with the use of Pradaxa when he prescribed it to Mr. Ridings. *See* SUF ¶¶ 17 (Gupta (5/14/18) Dep. at 49:14-22 ("Q. Did you understand at the time that you prescribed Pradaxa for Mr. Ridings that Pradaxa could cause serious and sometimes fatal bleeding? A. Yes. Q. Did you understand that it could cause a patient to experience an intracerebral hemorrhage? A. Yes.")). He knew that there was no

[8] BI also believes that Pradaxa's bleed warnings are adequate as a matter of law. *See, e.g., Johnston v. Upjohn Co.*, 442 S.W.2d 93, 95 (Mo. Ct. App. 1969) (where warnings are adequate as a matter of law, failure to warn cannot be established). However, given Dr. Gupta's testimony, the Court need not address that issue in order to grant summary judgment on Plaintiffs' failure to warn claims.

reversal agent for Pradaxa when he prescribed it to Mr. Ridings. SUF ¶ 18 (Gupta Dep. at 60:17-21 ("Q. And you understood at the time you prescribed Pradaxa for Mr. Ridings that there was no reversal agent or antidote available to reverse the anticoagulant effect of Pradaxa? A. Correct.")). Under these circumstances, no failure to warn on Defendants' part could have proximately caused Plaintiffs' alleged injuries, and summary judgment is warranted. *See Alpha Therapeutic*, 3 S.W.3d at 421 (holding manufacturer's alleged failure to warn could not be proximate cause of plaintiff's injuries because plaintiff's treating physicians were already aware of risk); *see also Kirsch*, 753 F.2d at 671-72.

B. Dr. Gupta stands by his prescribing decision, even when confronted with alleged warning inadequacies in his deposition.

Despite examination by Plaintiffs' counsel concerning alleged warning deficiencies for Pradaxa, Dr. Gupta stands by his prescribing decision. SUF ¶¶ 20, 23 (Gupta (5/14/18) Dep. at 130:24–131:3 ("Q. Okay. Knowing that Mr. Ridings sustained a subdural hematoma, do you still stand by your decision to have recommended that he take Pradaxa? A. I do."); Gupta (11/15/18) Dep. at 249:1-11 ("Q. Having read this article that's been marked as Plaintiff's Exhibit 3 [regarding P-gp inhibitors and potential increased Pradaxa exposure], does it change your decision about having prescribed Pradaxa for Mr. Ridings in 2012? A. No. No. Q. Do you -- after having seen this article and been asked questions about it, do you stand by your decision to have prescribed Pradaxa for Mr. Ridings in 2012 and 2013? A. Yes."). Plaintiffs, therefore, cannot establish causation on any failure to warn. *Kirsch*, 753 F.2d at 671 ("The plaintiff has the burden of showing that the absence of a warning caused the injury."). Plaintiffs presented no additional warning or information to Dr. Gupta that would have changed his prescribing decision. SUF ¶¶ 19-23. There is simply no proof that any different or additional warning would have made any difference here.

C. Plaintiffs' fraud, misrepresentation, warranty and Missouri Merchandising Practices Act claims fail for the same reasons as their failure to warn claims.

As noted in *Narain v. Boehringer Ingelheim Pharms., Inc.*, when a failure to warn claim cannot be sufficiently stated, claims for fraud and misrepresentation likewise fail because "these claims are based on the same facts" as the failure to warn claim. Ex. 20, Order Granting Defendants' Motion for Summary Judgment, No. CGC-16-553225 (Cal. Super Ct. Feb. 1, 2019). This is consistent with courts around the country that have held that misrepresentation, fraud, fraudulent concealment, breach of warranty and consumer fraud claims all fail if judgment is proper to defendant on a failure to warn claim.[9] This is so because "[i]f the learned intermediary doctrine could be avoided by casting what is essentially a failure to warn claim under a different cause of action . . . then the doctrine would be rendered meaningless." *Huskey*, 2014 U.S. Dist. LEXIS 92315, at *20 (quoting *Norplant*, 955 F. Supp. at 709).

IV. Alternatively, Plaintiffs' Failure to Warn Claim Is Preempted.

As explained above, "when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes." *Mensing*, 564 U.S. at 623-24. Because BI could not have independently changed Pradaxa's warnings to address Plaintiff's labeling criticisms, Plaintiff's warnings-based claims are preempted by federal law.[10]

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[9] *See Bellew v. Ethicon, Inc.*, No. 2:13-CV-22473, 2014 WL 6886129, at *5-6 (S.D. W. Va. Nov. 24, 2014) (dismissing claims for fraud, fraudulent concealment, negligent misrepresentation, breach of warranty, and Arizona Consumer Fraud Act); *Talley v. Danek Medical, Inc.*, 179 F.3d 154, 162-64 (4th Cir. 1999) (applying the learned intermediary doctrine to fraud and warranty claims under Virginia law); *In re Norplant Contraceptive Prods. Liab. Litig.*, 955 F. Supp. 700, 709 (E.D. Tex. 1997), *aff'd*, 165 F.3d 374 (5th Cir. 1999) (applying to fraud, affirmative representations, Deceptive Trade Practices Act, and other claims under Texas law); *Lachance v. Am. Home Products Corp.*, 2006 WL 89850, at *3 (W.D. Mo. Jan. 13, 2006) (granting motion for summary judgment on consumer law claim).

[10] The U.S. Supreme Court is currently considering the scope of federal preemption in *Merck Sharp & Dohme Corp. v. Albrecht*, *cert. granted* 138 S. Ct. 2705 (2018). The Supreme Court heard argument in

A. BI Could Not Have Independently Changed Pradaxa's Warnings After Approval and Before Plaintiff's Injury Given the Absence of Newly Acquired Information.

Warnings-based claims are preempted if the defendant pharmaceutical manufacturer would have needed FDA approval to add the warning that the plaintiff argues should have been included in the label. *See Wyeth*, 555 U.S. at 568; *Mensing*, 564 U.S. at 623–24; *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 814 (7th Cir. 2018) ("State laws requiring a label change are preempted unless the manufacturer could unilaterally add the new warning under the CBE regulation."). Manufacturers can implement a warning without FDA approval only in limited circumstances, pursuant to the "changes being effected" ("CBE") regulation. *Wyeth*, 555 U.S. at 568 (citing 21 C.F.R. § 314.70(c)(6)); *Mensing*, 564 U.S. at 614 (same). Here, Plaintiffs' warnings claims are barred because Plaintiffs have not met their burden of showing that "newly acquired information" exists to support a change to Pradaxa's label under the CBE regulation.

Labeling changes made pursuant to the CBE regulation must be based on "newly acquired information." *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699 (2d Cir. 2019) (quoting 21 C.F.R. § 314.70(c)(6)(iii)); *see also In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 41–42 (1st Cir. 2015). Federal regulations define "newly acquired information" as:

> [D]ata, analyses, or other information not previously submitted to the [FDA], which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

21 C.F.R. § 314.3(b).

Albrecht on January 7, 2019, and the Supreme Court's forthcoming decision in that case could impact this issue further.

The plaintiff bears the burden of showing "a labeling deficiency that [Defendants] could have corrected using the CBE regulation." *Gibbons*, 919 F.3d at 708 (quoting *In re Celexa.*, 779 F.3d at 41).[11] In the absence of a showing of such newly acquired information, claims that a company should have changed its warnings based on information already in the possession of the FDA are preempted by federal law.[12]

Here, Plaintiffs have failed to allege with specificity or produce any evidence that BI was in possession of newly acquired information after the FDA approved Pradaxa in October 2010 and prior to Plaintiff's alleged injury in July 2013 that would have enabled BI to make any unilateral changes to Pradaxa's warning without prior FDA approval. Plaintiffs' failure to meet his burden of demonstrating newly acquired information ends the preemption analysis.

Indeed, Plaintiffs' warnings criticisms are based on data and analyses that were provided by BI to the FDA during the Pradaxa approval process. Since before Pradaxa's approval, BI has communicated extensively with the FDA about Pradaxa's safety and efficacy. *See, e.g.*, Ex. 1, Clinical Overview. Plaintiffs' own regulatory expert, Laura Plunkett, has repeatedly conceded that all relevant data was submitted to the FDA prior to approval.[13] And at the time of Pradaxa's

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[11] Indeed, the plaintiff's complaint must specifically identify such newly acquired information. *See Gibbons*, 919 F.3d at 708.

[12] *See, e.g.*, *Gibbons*, 919 F.3d at 708 (plaintiff's "do not plausibly allege the existence of newly acquired information that could have justified Defendants' revising the Eliquis label through the CBE regulation"); *Dolin*, 901 F.3d at 815–16 (where plaintiff failed to offer evidence of newly acquired information, and "the undisputed evidence shows that the FDA was aware of the nature of the data it received from [defendant]," plaintiff's failure-to-warn claim was preempted); *In re Celexa*, 779 F.3d at 42–43 (ruling that plaintiff's California state law claims were preempted given lack of newly acquired information); *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 185 F. Supp. 3d 761, 769 (D.S.C. 2016) ("[A]ny claim that a drug label should be changed based on information previously submitted to the FDA is preempted because the CBE regulation cannot be used to make a label change based on such information.").

[13] *See, e.g.*, Ex. 21, *Knight v. Boehringer Ingelheim* Trial Tr. vol. 3, 570:23–571:9 (Oct. 5, 2018), ECF No. 189 ("Q. . . . Boehringer shared every one of those studies with the FDA, both the preclinical and the clinical studies, correct? A. That's my understanding, yes. Q. And when BI submitted Pradaxa for approval by the FDA, the FDA got all of the raw data from the RE-LY trial, correct? A. Yes, they were given the raw data. Q. Okay. And BI also submitted all of the PK data for Pradaxa that served as the basis

approval, the FDA issued numerous review memos making clear its understanding of the medicine's risks that Plaintiff now claims should have been warned about in Pradaxa's label. *See, e.g.*, Ex. 2, Summary Review; Ex. 3, Office Director Memo; Ex. 4, Medical Review(s); Ex. 5, Clinical Pharmacology and Biopharmaceutics Review(s).

In particular, Plaintiffs' failure-to-warn allegations regarding the bleeding risk associated with higher plasma concentrations of Pradaxa and the need to monitor or measure plasma levels are based entirely on RE-LY trial data on plasma concentrations and patient outcomes. All of that data was submitted to the FDA prior to Pradaxa's approval, *see, e.g.*, Ex. 1, Clinical Overview, at 23–25, 30–35, 94; and the FDA carefully reviewed and analyzed that data before approving the medicine, *see, e.g.*, Ex. 5, Clinical Pharmacology and Biopharmaceutics Review(s), at 9, 17–18; Ex. 3, Office Director Memo, at 1–2; Ex. 6, Kevin Krudys, Exposure Response Analysis of Dabigatran in RE-LY. Plaintiffs' regulatory expert, Dr. Plunkett, has testified that "having reviewed the data, this blood plasma data, concentration data, exposure data, the FDA concluded that routine monitoring was not required" with Pradaxa.[14] Likewise, Plaintiffs' other failure-to-warn allegations—including those regarding the risks in patients who are elderly and renally impaired—are not based on any information newly acquired after BI's pre-approval submissions to the FDA.

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for . . . the Reilly exposure paper that you talked about yesterday, correct? A. The raw data went in, yes, that is true."); Ex. 22, *Bedsole v. Boehringer Ingelheim* Trial Tr. (Sept. 20, 2018 PM) 52:7–11, 53:9–11 ("Q. Let's talk about the FDA and the information that the FDA had. As part of the approval process for Pradaxa, Boehringer took all that blood concentration data and provided it to the FDA. Correct? A. Yes. The data was submitted. . . . Q. Before [the FDA] approved the medicine, they had all the blood concentration data. Correct? A. Yes, they did.").

[14] Ex. 23, *Gallam v. Boehringer Ingelheim* Trial Tr. 85:4–15 (Apr. 20, 2018); *see also* Ex. 24, *Boone v. Boehringer Ingelheim* Trial Tr. 112:23–113:2 (Mar. 1, 2018 AM) (testifying that "the FDA specifically considered before approving Pradaxa the question of monitoring").

Nothing changed with respect to these facts after Pradaxa's approval and prior to Plaintiff's alleged injury.[15] Nor is there any allegation that BI concealed specific information from the FDA when it submitted its NDA or at any time thereafter during the course of the drug approval process. Because Plaintiffs fail to identify any newly acquired information that would have enabled BI to change Pradaxa's warning as Plaintiffs allege that state law requires, Plaintiffs' warnings-based claims are preempted and summary judgment should be granted.

B. There Is Clear Evidence that the FDA Would Not Have Approved Plaintiffs' Proposed Warnings.

Even if BI could have implemented Plaintiffs' proposed labeling changes through the CBE process without any "newly acquired information"—and, as explained above, it could not have—the Court should still grant summary judgment on Plaintiffs' warnings-based claims for a second and independent reason: there is "clear evidence" that the FDA would have rejected any such labeling changes.

Because the FDA "retains authority to reject labeling changes," a pharmaceutical manufacturer may still—even after a plaintiff has identified "newly acquired information"—establish an impossibility preemption defense through "clear evidence that the FDA would not have approved a change" to the label. *Wyeth*, 555 U.S. at 571; *see also Mensing*, 564 U.S. at 624 n.8; *Dolin*, 901 F.3d at 812 ("[E]ven if [defendant] had newly acquired information along these lines, [defendant] can still succeed on its preemption defense if there is clear evidence that the FDA would have rejected the . . . warning that plaintiff argues was tortiously omitted."); *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010) ("[A] court cannot

[15] Any information "newly acquired" after Plaintiff's alleged injury in July 2013 cannot support Plaintiff's claim, given that such information would provide a basis for changing Pradaxa's warnings only *after* Plaintiff's injury.

order a drug company to place on a label a warning if there is 'clear evidence' that the FDA would not approve it.").

Here, there is clear evidence that the FDA would have rejected the warnings proposed by Plaintiffs given that: (a) the FDA did in fact reject various such warnings proposed by BI, and (b) the FDA has made clear its view that the plasma monitoring and dose adjustment proposed by Plaintiffs should not be required.

1. The FDA's Rejection of BI's Proposed Warnings Is Clear Evidence that the FDA Would Not Have Approved a Labeling Change.

Many of the warnings now proposed by Plaintiffs were actually submitted to the FDA by BI and specifically rejected by the FDA:

- Bleeding risk related to plasma concentrations. Prior to approval, BI proposed warning language regarding Pradaxa plasma concentration levels, as measured by the aPTT test, that were associated with a higher risk of bleeding: "In patients who are bleeding, the aPTT test maybe [sic] useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity to dabigatran etexilate. An aPTT greater than 80 sec is associated with a higher risk of bleeding." Ex. 25, E-mail from Michelle Kliewer, Director, BI Drug Regulatory Affairs, to Alison Blaus, FDA Ctr. for Drug Evaluation & Res. (Sept. 27, 2010) (BIPI-PRA-0001916229) ("Sept. 27, 2010 Kliewer E-mail") and Ex. 26, Pradaxa Proposed Prescribing Information, at 4 (Sept. 27, 2010) (BIPI-PRA-0001916232) ("Sept. 27, 2010 Proposed Prescribing Information"). The FDA rejected that language, deleting it from BI's proposed label altogether. Ex. 27, E-mail from Alison Blaus to Michelle Kliewer (Oct. 8, 2010) (BIPI-PRA-0001911086) ("Oct. 8, 2010 Blaus E-mail") and Ex. 28, Pradaxa Proposed Prescribing Information, at 4 (Oct. 8, 2010) (BIPI-PRA-0001911087) ("Oct. 8, 2010 Proposed Prescribing Information").

- Increased risk based on age. BI also proposed language regarding the increased risk of stroke and bleeding with Pradaxa in the elderly: "The risk of stroke and bleeding increased with advancing age in all treatment groups." Ex. 29, Pradaxa Proposed Prescribing Information, at 5 (Oct. 18, 2010) (BIPI-PRA-0001908284). In response, the FDA revised that language to emphasize that Pradaxa's risk-benefit profile was favorable even in older patients: "The risk of stroke and bleeding increase with age, but the risk-benefit profile is favorable in all age groups." Ex. 30, E-mail from Alison Blaus to Michelle Kliewer (Oct. 19, 2010) (BIPI-PRA-0001908025) and Ex.48, Pradaxa Label, at 4 (Oct. 2010) (BIPI-PRA-0001908026).

- Recommendation for lower dose in high-risk patients (including the elderly and those with renal impairment). BI also proposed a recommendation that the lower 110 mg

dose of Pradaxa be considered for certain patients: "For those patients with a potentially higher risk of bleeding, (e.g., age ≥75 years, CHADS2 score of ≥3, moderate renal impairment (30 to 50 mL CrCL/min), concomitant treatment with P-gp inhibitors, or previous gastrointestinal bleed), a reduced dose of 110 mg twice daily may be considered." Ex. 25, Sept. 27, 2010 Kliewer Email and Ex. 21, Sept. 27, 2010 Proposed Prescribing Information, at 9. The FDA rejected that language, and declined to approve the 110 mg dose. Ex. 27, Oct. 8, 2010 Blaus E-mail and Ex. 23, Oct. 8, 2010 Proposed Prescribing Information at 12; *see also* Ex. 31, E-mail from Alison Blaus to Michelle Kliewer (Oct. 4, 2010) (BIPI-PRA-0001914206) (directing BI to "please delete all dabigatran 110 information" from the proposed label). Various regulatory documents make clear that the FDA reached the conclusion that the 150 mg dose was appropriate for all patient groups (other than patients with severe renal impairment, for whom the 75 mg dose is recommended).[16]

- Increased risk of bleeding in elderly patients taking certain concomitant medications. When BI proposed a warning that, "[w]ith concomitant intake of antiplatelets or P-gp inhibitors in patients aged ≥75 years, the risk of major bleeding, including gastrointestinal bleeding, increases," the FDA rejected that language as well. Ex. 32, E-mail from Alison Blaus to Michelle Kliewer (Oct. 17, 2012) (BIPI-PRA-0025890191) and Ex. 33, Pradaxa Proposed Prescribing Information, at 4 (Oct. 2012) (BIPI-PRA-0025890192). The FDA explained its rationale for rejecting this proposed warning: "The changes proposed [by BI] are all independent risk factors for bleeding and do not need to be called specifically in the label. Also, we do not want [this section of the label] to become too long to be useful." Ex. 34, E-mail from Alison Blaus to Michelle Kliewer (Oct. 24, 2012) (BIPI-PRA-0025888957).

- Risk of fatal bleeding regardless of location. Additionally, BI proposed a warning that bleeding with Pradaxa could be fatal, regardless of location: "Major or severe bleeding may occur at any site and regardless of location may lead to disabling, life-threatening or fatal outcomes." Ex. 25, Sept. 27, 2010 Kliewer E-mail and Ex. 26, Sept. 27, 2010 Proposed Prescribing Information, at 4. The FDA rejected that language and replaced it with the language that appears in the label today: "PRADAXA can increase the risk of bleeding and cause significant and sometimes fatal bleeding." Ex. 27, Oct. 8, 2010 Blaus E-mail and Ex. 28, Oct. 8, 2010 Proposed Prescribing Information, at 4.

[16] *See, e.g.*, Ex. 16, Beasley et al., at 1789 (stating that the FDA was "unable to find any population for whom the availability of a lower [110 mg] dose would improve dabigatran's benefit-risk profile"); Ex. 2, Summary Review, at 14 ("It is clear that the higher [150 mg] dose is what the vast majority of patients, if not all patients, should receive."); Ex. 3, Office Director Memo, at 4 ("In summary, if there is a population that would be better off on a dose of 110 mg, it has not been clearly identified.").

The FDA's rejection of these warnings constitutes clear evidence under *Wyeth* that the FDA would not have approved Plaintiffs' proposed warnings.[17]

2. The FDA's Rejection of Plasma Monitoring Constitutes Clear Evidence that the FDA Would Not Have Approved Labeling Recommending Monitoring.

As explained in BI's motion to exclude Dr. Plunkett, any monitoring opinion lacks a connection to the case because no expert opines that monitoring would have altered the outcome for Mr. Ridings. In any event, the FDA has repeatedly made clear its position that plasma monitoring and dose adjustment based on such monitoring are not required with Pradaxa, providing an independent basis for finding clear evidence that the FDA would not have approved Plaintiffs' proposed monitoring warnings.

Since prior to Pradaxa's approval, the FDA has conducted its own analyses regarding Pradaxa plasma concentrations and the potential utility of monitoring,[18] spoken publicly on the issue,[19] and participated in broader scientific discussions, focused not just on Pradaxa but on all

[17] *See, e.g.*, *Dolin*, 901 F.3d at 816 (ruling as matter of law that FDA's rejection of warnings proposed by defendant constituted "clear evidence" under *Wyeth* "that the FDA would have rejected the warning that plaintiff seeks under [state] law"); *Rheinfrank v. Abbott Labs., Inc.*, 680 F. App'x 369, 385 (6th Cir. 2017) ("Because the FDA twice refused [defendant's] attempts to strengthen [the drug's] label . . . [plaintiff's] failure-to-warn claim is preempted by federal drug labeling law."); *Robinson*, 615 F.3d at 873 (recognizing as "clear evidence" FDA's rejection of proposed warnings regarding risk at issue, and noting that "it would be odd to think that [defendant] had a legal duty to guarantee against a risk that the FDA thought not worth warning against"); *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1173–74 (S.D. Cal. 2016) (ruling that claims were preempted based on FDA's repeated refusals to find causal connection between drug and injury, and stating that "the most persuasive evidence in support of preemption is the FDA's February 27, 2014, publication in the New England Journal of Medicine" explaining its position).

[18] *See, e.g.*, Ex. 5, Clinical Pharmacology and Biopharmaceutics Review(s), at 9, 17–18; Ex. 3, Office Director Memo, at 1–2.

[19] *See, e.g.*, Ex. 7, Advisory Comm. Tr. 164:10–16 ("So there are some factors that will change concentrations quite a bit, but we didn't see a need for a monitoring the concentration because we saw in a study, favorable results in all subgroups. So it didn't seem like we found something strong that we needed to monitor concentrations and adjust in a certain subset of the population."); Ex. 6, Krudys, Exposure Response Analysis of Dabigatran in RE-LY.

novel oral anticoagulants.[20] Having repeatedly considered this issue, the FDA has never once amended its view that plasma monitoring and dose adjustment based on plasma levels are not required with Pradaxa.[21] To the contrary, the FDA has continued to affirm Pradaxa's safety and efficacy on a fixed-dose basis without any requirement for plasma monitoring. Just last year, following a series of think-tank meetings hosted by the Cardiac Safety Research Consortium regarding Pradaxa and other novel oral anticoagulants, four senior FDA scientists co-authored an article stating the "consensus position[]" that "[r]outine PK-PD measurements to guide NOAC [novel oral anticoagulant] dosing cannot currently be recommended." Ex. 35, Chan et al., at 66.

Consistent with this position, and as discussed *supra*, the FDA has considered and rejected warnings relating to Plaintiffs' monitoring theory. In particular, the FDA rejected proposed labeling regarding plasma concentration levels "associated with a higher risk of bleeding," as well as warnings about increased risks in those patients likely to have higher plasma concentrations, such as the elderly and patients with impaired renal function.[22]

In addition, the FDA's decision not to approve the lower 110 mg dose—which, if Plaintiffs' monitoring theory were accepted, would be the recommended dose for certain high-risk patients—provides further evidence that the FDA would not approve Plaintiffs' proposed monitoring warnings. In declining to approve the 110 mg dose, the FDA addressed the possible benefits of reducing the dose of Pradaxa in patients with higher plasma concentrations, but concluded that "even in a population exposed to relatively high concentrations of dabigatran, the 150-mg dose had a superior benefit–risk profile." Ex. 16, Beasley et al., at 1789.[15]

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[20] *See, e.g.*, Ex. 35, Chan et al., *Is There A Role For Pharmacokinetic/ Pharmacodynamic Guided Dosing For Novel Oral Anticoagulants?*, 199 Am. Heart J. 59 (2018).
[21] *See, e.g.*, Ex. 3, Office Director Memo, at 4 ("Follow-up of anticoagulant activity is generally not needed.").
[22] *See* Ex. 27, Oct. 8, 2010 Blaus E-mail and Ex. 28, Oct. 8, 2010 Proposed Prescribing Information at 4, 12.

The regulatory record above constitutes clear evidence under *Wyeth* that the FDA would not have approved Plaintiffs' proposed monitoring warnings. Since Pradaxa's approval, BI has continued to provide the FDA with additional information regarding the medicine's safety—including the same information upon which Plaintiff relies in support of his plasma monitoring allegations against BI. But even after receiving this information, the FDA has never required a change to Pradaxa's warnings to require plasma monitoring or dose titration based on such monitoring, reflecting a rejection of the substance of Plaintiffs' proposed warnings.

In particular, following a series of *BMJ* articles discussing plaintiffs' allegations, BI made additional submissions to the FDA regarding the dose-titration analysis that BI conducted to explore whether Pradaxa's benefit-risk profile could be improved further. BI provided the FDA with the same submissions that BI made to European regulators, detailing dose-titration modeling and simulations that BI conducted in 2012, BI's subsequent efforts to validate the initially-promising analysis, and BI's ultimate conclusion that the analysis could not be validated and thus did not require any change to Pradaxa's labeling or dosing recommendations. Among other submissions, BI communicated the following information to the FDA:

- On July 24, 2014, following the publication of articles in the *BMJ* alleging that BI had improperly withheld the results of its internal dose-titration analysis from regulators, BI sent the FDA the *BMJ* articles and BI's press release responding to the allegations made in those articles. *See* Ex. 36, E-mail from Heidi Reidies, Exec. Dir., BI Drug Regulatory Affairs, to Alison Blaus, and attachments (July 24, 2014) (BIPI-PRA-0062002313–38). The *BMJ* articles were heavily influenced by Pradaxa plaintiff lawyers and parroted their allegations; BI's submission of these articles thus put Plaintiffs' allegations directly before the FDA. In response, the FDA continued to approve Pradaxa's warnings without endorsing any of Plaintiffs' allegations.

- On August 18, 2014, BI submitted to the FDA a copy of the company's LEG 43 submission to the European Medicines Agency (EMA) detailing the "company position regarding fixed versus adjusted dosing of dabigatran." Ex. 37, Letter from Heidi Reidies to Norman Stockbridge, Dir., FDA Ctr. for Drug Evaluation & Res., and attachments, at On December 12, 2014, BI shared with the FDA a follow-up submission BI had made to EMA regarding monitoring and dose-titration issues. *See* Ex. 38, Letter from Dawn Collette, BI Drug Regulatory Affairs, to Norman

Stockbridge, and attachments (Dec. 12, 2014) (BIPI-PRA-0062433536–89). This submission included an overview of BI's dose-titration analysis and its unsuccessful attempts to validate the model, *id.* at BIPI-PRA-0062433537–38; a 33-page "comprehensive review" of "all information available to [BI] and relevant to the question whether dose titration and therapeutic drug monitoring (TDM) may add clinically relevant benefit compared to fixed dosing in patients treated with dabigatran," *id.* at BIPI-PRA-0062433544; and an expert opinion supporting BI's conclusions, *id.* at BIPI-PRA-0062433583–89.

- On August 19, 2015, BI sent the FDA additional information regarding BI's interactions with EMA on this issue, including BI's latest submission. *See* Ex. 39, E-mail from Michelle Kliewer to Alison Blaus, and attachments (Aug. 19, 2015) (BIPI-PRA-0062118776–94) (Exs. 37, 38, and 39 to 2017 Kliewer Dep.).

- On February 9, 2016, BI sent EMA's final LEG 43 report to the FDA. *See* Ex. 40, E-mail from Michelle Kliewer to Alison Blaus, and attachments (Feb. 9, 2016) (BIPI-PRA-0062077672–74). Referring to BI's dose-titration analysis, EMA "endorsed" BI's conclusion "that the trial simulations based on the PK-response model had limitations making them inapplicable in predicting the dose-response differences between 110 mg bid and 150 mg bid," and agreed with BI that it "does not believe that available data such as the PK-response model support that routine monitoring of dabigatran anticoagulant activity would result in an enhanced balance between benefits and bleeding risks." *Id.*, BIPI-PRA-0062077674, at 17. EMA concluded that "currently the benefit-risk profile of Pradaxa treatment is positive," "[t]he size of the patient populations necessary to enter into studies investigating [therapeutic drug monitoring] of Pradaxa is regarded too large compared to the theoretical improvement in the benefit-risk profile to justify such studies," and "routine [therapeutic drug monitoring] of Pradaxa should not be recommended." *Id.*, BIPI-PRA-0062077674, at 63.

More than four years have now passed since the *BMJ* articles were published detailing plaintiffs' claims and BI first shared its dose-titration evaluations and other data and analyses with the FDA. Having had this information in its possession for years, the FDA has taken no action to update Pradaxa's labeling to require blood plasma monitoring or dose titration—as would be the FDA's responsibility if it was concerned about patient safety.[23] To the contrary, since BI sent its final EMA submission to the FDA in August 2015, the FDA has approved four new labels for Pradaxa—none of which contains a therapeutic range or recommends plasma

[23] *See* 21 U.S.C. § 355(o)(4)(A) (requiring FDA to "promptly" engage the drug's sponsor to amend the drug's labeling if FDA "becomes aware of new safety information . . . that [it] determines should be included in the labeling of the drug").

monitoring or dose titration.[24] The FDA's repeated affirmation of Pradaxa's safety and efficacy as described in the Pradaxa label, informed by this additional information provided by BI, constitutes clear evidence that the FDA would not approve Plaintiffs' proposed plasma monitoring warnings.

V. Plaintiffs' Negligence Claims Should Be Dismissed.

Plaintiffs' negligence-based claims are based on the same series of facts as her strict liability claims. Both require the same causation analysis. *Willard v. Bic Corp.*, 788 F. Supp. 1059, 1063 (W.D. Mo. 1991). As explained above in sections II and III, Plaintiffs cannot establish their strict liability design defect or warnings claims, and for the same reasons, summary judgment as to their negligence claim is proper.

VI. Plaintiffs Did Not Give the Required Pre-Suit Notice to Bring Warranty Claims.

Plaintiffs' breach of warranty claims fail for lack of the necessary pre-suit notice of the alleged breach. Missouri law required Plaintiffs to give notice of any alleged breach "within a reasonable time after" the breach is discovered. Mo. Rev. Stat. § 400.2-607(3)(a). Without such notice, Plaintiffs are "barred from any remedy." *Id.* Plaintiff failed to provide the required pre-suit notice and, therefore, her breach of warranty claims fail.

VII. The Loss of Consortium Claim is Derivative and Should Be Dismissed.

Because Plaintiffs' substantive claims are all without merit, the loss of consortium claim – which is derivative in nature – also fails. *Thompson v. Brown & Williamson Tobacco Corp.*, 207 S.W.3d 76, 112 (Mo. Ct. App. 2006) ("A consortium claim is a separate, distinct, and

[24] *See, e.g.*, Ex. 41, Pradaxa Label, § 2.2 (Mar. 2018) ("Generally, the extent of anticoagulation does not need to be assessed."); Ex. 42, FDA, NDA 022512/S-035 Supplemental Approval Letter at 1 (Mar. 13, 2018) (enclosing the March 2018 Pradaxa label and stating that the "[c]ontent of labeling must be identical to the enclosed labeling").

personal legal claim, and is derivative only in the sense that it must be occasioned by a spouse's injury.").

VIII. Plaintiffs Cannot Meet Their Burden to Establish Entitlement to Punitive Damages.

Summary judgment is appropriate for a claim of punitive damages.[25]

To prevail on a claim for punitive damages in a product liability claim in Missouri, "t]here must be some element of outrage to justify punitive damages." *Burnett v. Griffith*, 769 S.W.2d 780, 789 (Mo. 1989). In addition, to recover punitive damages, a plaintiff must show "a willful, wanton or malicious culpable mental state on the part of the defendant." *Id*. at 789. A plaintiff can establish this requisite culpable mental state by showing either that the defendant committed an intentional wanton, willful, outrageous act or that defendant acted with reckless disregard for the plaintiff's rights and interests. *Blanks v. Fluor Corp.*, 450 S.W.3d 308.[26] Under Missouri law, punitive damages are sparingly permitted, and whether such damages are appropriate in each case is a question of law for the trial court. *Jone v. Coleman Corp.*, 183 S.W.3d 600, 610 (Mo. Ct. App. 2005). Plaintiffs cannot meet this standard here.

From the moment Pradaxa was approved by the FDA, the prescribing information for the medicine has carried numerous warnings directed at physicians regarding the risks of bleeding, including subdural hematoma. The warning clearly stated that no reversal agent existed for

[25] While BI believes that Connecticut law should govern the issue of punitive damages, BI recognizes that the Eighth Circuit has held that the place where the injury occurred is presumptively the state with the most significant relationship whose punitive damage law would apply. *Winter v. Novartis, Inc.*, 739 F.3d 405 (8th Cir. 2014) (noting that while a corporation's home state has an interest in applying its law to its corporate residents, "Missouri has a strong interest in applying its punitive damages laws to deter conduct by corporations doing business in Missouri that harms Missouri residents."). In any event, Plaintiffs cannot establish the requisite standard of conduct to recover punitive damages under either state's law.

[26] Similarly, under Connecticut law, a plaintiff must "prove[] that the harm suffered was the result of the product seller's reckless disregard for the safety of product users, consumers or others who were injured by the product." Conn. Gen. Stat. § 52-240b. "[P]unitive damages may be awarded only for outrageous conduct, that is, for acts done with a bad motive or with a reckless indifference to the interests of others." *Triangle Sheet Metal Works, Inc. v. Silver*, 154 Conn. 116, 128 (1966) (internal quotation marks omitted).

Pradaxa at the time of Mr. Ridings's prescription. So, too, concomitant use of medications, including P-gp inhibitors, was reflected in the warnings.

To impose punitive damages on a manufacturer of an FDA-approved medicine who explicitly warned of the risk of the very injury suffered would render any standard of reckless disregard meaningless. Construing Missouri law, in *DeLuryea v. Winthrop Laboratories*, 697 F.2d 222, 230 (8th Cir. 1983), the Eighth Circuit found that the defendant drug manufacturer failed to adequately warn of dangers concerning tissue damage and drug dependence, but that punitive damages were not warranted because "warnings were given concerning both tissue damage and drug dependence." Because of that, plaintiff could not establish malice, wantonness or reckless indifference by defendant as a matter of law, and the trial court correctly declined to submit the issue to the jury. In *Jone v. Coleman Corp.*, 183 S.W.3d 600, 610 (Mo. Ct. App. 2005), the court affirmed the trial court's dismissal of the claim for punitive damages because the defendant's product contained a warning that alluded to the danger that caused plaintiffs' injury, and therefore "did not willfully or consciously disregard the safety of the consumers" as a matter of law. Numerous other courts have held similarly. *See In re Levaquin Prods. Liab. Litig.*, 700 F.3d 1161, 1170-71 (8th Cir. 2012) (Minnesota law) (evidence did not meet standard of conscious or intentional disregard or indifference to consumer safety because risk was contained in warning); *Scharff v. Wyeth*, No. 2:12-CV-220-WKW, 2012 WL 3149248, at *9 (M.D. Ala. Aug. 1, 2012) (punitive damages "should not go to the jury when a manufacturer took steps to warn plaintiff of the potential danger that injured him; those facts bar a finding that defendant was consciously indifferent.") (quoting *Toole v. McLintock*, 999 F.2d 1430, 1436 (11th Cir. 1993); *Salvio v. Amgen Inc.*, No. 2:11-CV-00553, 2012 WL 517446, at *8 (W.D. Pa. Feb. 15, 2012) ("claims for punitive damages are unfounded where a manufacturer-defendant warns of

the potential danger that resulted in injury to a plaintiff"); *Dudley v. Bungee Int'l Mfg. Corp.*, No. 95-1204 (4th Cir. Jan. 31, 1996) 1996 WL 36977, at *3 (Table) (finding that "since [defendant] warned of the potential danger that injured [plaintiff], it exhibited some care for his safety" and thus "an award of punitive damages was not warranted under a failure to warn theory").

The same holds true here. Plaintiffs cannot show BI acted with reckless disregard for patient safety when the Pradaxa label addressed the risks of injury that Plaintiffs claim and has been re-approved repeatedly over time. The FDA continues to confirm the safety and efficacy of Pradaxa.[27] This is particularly true when the substance of Plaintiffs' allegations has been discussed openly in the scientific literature, including by plaintiff lawyer surrogates in publications from 2014 in the British Medical Journal discussing documents produced in the prior MDL litigation.[28] Despite this airing of plaintiff lawyer views, none of Plaintiffs' allegations has been adopted by any regulator in the world, including the FDA. As recently as

[27] *See* Food & Drug Admin., FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin (May 13, 2014) ("as a result of our latest findings, we still consider Pradaxa to have a favorable benefit to risk profile and have made no changes to the current label or recommendations for use. Patients should not stop taking Pradaxa (or warfarin) without first talking with their health care professionals.") (emphasis added), *available at* http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm.

[28] *See, e.g.*, Ex. 43, *Dabigatran: how the drug company withheld important analyses*, 349 BMJ g4670 (2014), at 1 (discussing "information about dabigatran disclosed through previously confidential internal company documents released during litigation in the US"); Ex. 44, *Dabigatran and statins: faith, hype, and transparency*, 349 BMJ g4793 (2014), at 1 (discussing "[c]ompany documents revealed in the course of US litigation"); Ex. 45, *Concerns over data in key dabigatran trial*, 349 BMJ g4747 (2014), at 1 (alleging that "[d]ocuments released during US litigation . . . show how Boehringer Ingelheim, the makers of dabigatran, failed to share with regulators information on how monitoring plasma levels of the drug and subsequent dose adjustment could reduce risk of major bleeds"); *id.* at 2 ("In the process of this litigation, plaintiffs' lawyers pointed out that some cases of fatal bleeding did not seem to have been counted in either the original analysis or the FDA mandated review."); Ex. 46, *The trouble with dabigatran*, 349 BMJ g4681 (2014), at 1 (claiming that "[a]dditional data from recent US lawsuits alleges that Boehringer did not adequately warn patients of the bleeding risks of dabigatran," and that "[l]itigation revealed internal documentation that the company failed to disclose that monitoring might reduce risk of stroke and bleeding"); Ex. 47, *Dabigatran, bleeding, and the regulators*, 349 BMJ g4517 (2014), at 2 (discussing an "internal Boehringer document made public in civil litigation"); *id.* at 4 (discussing details of a "Boehringer unpublished simulation model . . . based on the RE-LY sub-study and released during US litigation proceedings"); *id.* at 5 n.11, n.30 (citing Bates-stamped internal BI company documents produced during the course of litigation).

2018, a group of industry, medical, and FDA authors declared that "[r]outine PK-PD measurements to guide NOAC dosing cannot currently be recommended because of the lack of reliable tests, lack of clinical evidence of benefit, and lack of data to guide appropriate dosing." *See* Ex. 35, Chan et al., *Is there a role for pharmacokinetic/phramacodynamic-guided dosing for novel oral anticoagulants?*, 199 Am. Heart J. 59, 66 (2018). Plaintiffs' punitive damages claim thus depends on the implicit argument that the FDA and every other regulator in the world has acted with the same reckless disregard for patient safety that she accuses BI of demonstrating. This assertion is as meritless against the regulators as it is against BI.

Because Plaintiffs have no evidence that they are entitled to punitive damages here, summary judgment is proper on this claim.

CONCLUSION

For all of these reasons, BI is entitled to summary judgment on all of Plaintiffs' claims. Alternatively, should the Court determine that any claim survives summary judgment, BI is entitled to summary judgment on Plaintiffs' claim for punitive damages. BI requests any such relief, both general and special, to which the Court deems it entitled.

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that on May 13, 2019 the foregoing was filed electronically with the Clerk of Court to be served by operation of the Court's electronic filing system on all counsel of record.

/s/ Timothy J. Davis